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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/292,723	04/15/1999	CAROL READHEAD	P0741795	3964

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Edward G. Poplawski, Esq.
Sidley Austin Brown & Wood
555 West Fifth Street
Los Angeles, CA 90013-1010

EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 01/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/292,723	Applicant(s) READHEAD ET AL.	
	Examiner Joseph Woitach	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *133-195* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *133-195* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 April 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph T. Woitach** and the group art unit is now **1632**.

Applicants' amendment filed October 3, 2001, paper number 16, has been received and entered. Claims 1-62, 75-82, 94-101 and 107-117 have been canceled. Claims 133-195 have been added. In addition, Applicants' supplemental amendment filed October 19, 2001, paper number 17, has been received and entered. The specification has been amended. Claims 133-195 are pending and currently under examination.

Declaration

The Declaration of Dr. Carol W. Readhead under 37 CFR 1.132 filed October 3, 2001, Exhibit A attached to paper number 16, has been received and entered. The declaration will be discussed in detail in the 35 USC 112, first paragraph, rejection as it applies to newly added claims 133-195.

Claims

Claims 136, 172 and 184 are objected to for the following informalities: It appears that claims have editing notations still present in the claim. For the sake of compact prosecution, the claim will be read with the intended edits made.

Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over copending Application No. 09/191,920 is withdrawn.

It is noted that 09/191,920 has been allowed and is now US Patent No. 6,316,692. Applicants have filed a Terminal Disclaimer October 3, 2001, paper number 15, which has obviated the rejection.

Claims 133-195 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 124-139 and 157-159 of co-pending Application No. 09/272,443.

Applicants have indicated that upon the finding of allowable subject matter in 09/272,443 a terminal disclaimer will be executed to the allowable subject matter in the present application. See Applicants' amendment, page 17.

Applicants' willingness to file a terminal disclaimer over 09/272,443 is noted, however the filing of a terminal disclaimer can not be held in abeyance. Absent the filing of a terminal disclaimer, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 133-195 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants point out the claims 133-195 are directed to a polynucleotide containing a cyclin A1 promoter obviating the portion of the previous rejection regarding the use of any stem cell specific promoter. With respect to claim 181-195, Applicant point out that claims are directed to use of mice and obviates the portion of the previous rejection the generation of any transgenic mammal. With respect to claims 133-180 Applicants assert that these claims are enabled for all non-human mammals. Applicants argue that Examiner has ignored the art in reference to positive statements for the usefulness of animal models. Moreover, Applicants argue the usefulness of murine models for transgenesis in other mammal models providing several references in support of use of transgenic mouse models for human diseases. See Applicants' amendment pages 18-19 and Exhibit B-E. Applicants agree that methods for transfecting male germ cells in the past have been largely unsuccessful as shown in Sato *et al.*, Lavitrano et al. and Brinster. In addition, Applicants have supplied a Declaration of Dr. Carol W. Readhead under 37 CFR 1.132, demonstrating that a letivirus particle injected into the seminiferous tubules of the testis in a mouse is capable of producing genetically modified spermatogonia. The mice containing the transduced spermatagonia were capable of producing litters containing the marker gene for greater than 20 weeks. See Applicants' amendment pages 22-22 and Exhibit A. Applicants' arguments have been fully considered but not found persuasive.

Examiner agrees with Applicant that murine models are useful, however the basis of the rejection is not utility, it is the predictability of transgene behavior. The instant specification

demonstrates that the specific cyclinA1 promoter can be used for expression of a marker gene in the germ cells of a mouse, however there is no nexus that this construct will function in the same manner in other mammals. The art recognizes that transgene behavior is unpredictable and absent evidence to the contrary there is no indication that the results presented for the mouse are representative of function in other mammals. The references supplied as Exhibits B-E indicate murine models exist and may be useful, however they do not support that transgene behavior is predictable. For example, the are several art recognized murine models generated for Alzheimer disease (as reviewed by Duff *et al.* Exhibit E), however among the various models none produce the characteristic plaques seen in humans. Further, Duff *et al.* indicates that 'many of the mice do not completely replicate the human disease they are intended to model' (in provided abstract). Other exhibits only support the potential utility of future or potential murine models. In addition, it should be pointed out that the methods are directed to isolating stem cells. At the time of filing of the instant application, stem cells from the mouse were the only mammal from which stem cells were successfully isolated. As recognized by one of skill in the art, the specification defines a stem cell as a totipotent cell, however practicing the methods as presently recited would only result in a pluripotent germ cells from a mammal. Because stem cells have been reproducibly isoalted from mice, Examiner would concede that the methods are enabled for isolating stem cells from a mouse.

The art as exemplified by Sato *et al.*, Lavitrano *et al.* and Brinster, clearly indicates that the ability to simply transfect/transduce male germ cells was unpredictable at the time of the

claimed invention. The specification teaches various methods for the *in vivo* transfection of germ cells, among them the *in vivo* transduction of spermatogonia using lentivirus carrying a reporter gene (Example 14), however the results presented in the specification did not clearly indicate that the methodology resulted in the successful or reproducible genetic modification of germ cells. The Declaration of Dr. Carol W. Readhead indicates that following the same method steps as set forth in Example 14, the resulting transduced mice are capable of generating offspring with the transduced marker gene over a course of 20 weeks (summarized in Table 1). These results clearly indicate that methods which use of lentivirus transduction with polybrene results in the successful and reproducible genetic modification of male germ cells. In view of the evidence of record, Examiner would agree that Applicants have provided the evidence and necessary guidance which provides a nexus between the unpredictability in the art for the transfection of male germ cells and methodology which specifically uses lentivirus and polybrene for the transduction of male germ cells. Claims reciting these limitations would be found fully enabled, however, the instant claims encompass broader limitations and are not limited to only this initial transduction of germ cells. Further, the experiments and evidence of record support that the cyclin A1 promoter is functional in germ cells, however there is no indication that this promoter is functional in stem cells. Even if the promoter is functional in stem cells, the evidence would suggest then that the promoter is not useful in isolating stem cells through use of the promoter activity because its activity would also be indicative of other cell types.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required one of skill in the art undue experimentation to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 133-195 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 133, 149, 165 and dependent claims are unclear and confusing in the recitation of 'a selectable transgenic stem cell' because what is selected or selectable about the stem cell is not clearly defined. Further, the claim indicates that a selectable marker is expressed in a germ cell, however there is not connection between the germ cell and a stem cell.

Claims 134, 135 142 are confusing because it depends on a claim for obtaining transgenic stem cells however it seems directed to generating a transgenic mammal. Claim 134 does not further limit claim 133.

Claims 137 and 151 are unclear and confusing because insulator elements do not prevent methylation, it is the primary polynucleotide sequence which dictates whether the sequence will be methylated.

Claim 141 is unclear because it is dependent on claim 133, a method for isolating stem cells, though it is not clear how the development of a gamete is related to isolating a transgenic stem cell.

Claim 145 is confusing because a stem cell is not the same as a germ cell. It is unclear what the claim intends to encompass, a stem cell or a germ cell.

Claim 146 seems incomplete because it is directed to a transgenic mammal containing a transgenic stem cell of claim 144, however it is unclear how the stem cell is inserted into said mammal. Further, it is noted that a transgenic animal contains a transgene in its germ cells and its somatic cells.

Claims 147 and 148 are vague and unclear because the method is not 100% effective in transfection efficiency, and so it is unclear if the claim is directed to only the sperm containing a transgene or at low efficiency, if the claim would also encompasses sperm/semen from a wild mammal. Further, given that normal sperm is produced one would expect that the breeding would also produce a normal wild type mammal. More clearly indicating that the transgene is present would obviate the basis of the rejection.

Claim 158 is confusing because a stem cell is totipotent, not bipotent or monopotent. Further, absent somehow directly assaying the resulting cells, it is unclear how one would identify the cell is a pluri-, multi-, bi- or mono-potent cell.

Claims 167 and 176 are confusing because a stem cell is totipotent not those recited in the claim. Further, if the promoter can be used to isolate these cells, it is unclear how the promoter would be effective in any other method for any one specific cell type.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732.

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Deborah Crouch, can be reached on (703)308-1126.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630

Joseph T. Woitach